example, include urgent notices on the side effects of drugs.

The standard text can bring errors and omissions to the attention of the doctor editing it. This might be of value in both undergraduate and postgraduate training; indeed, it would bring new developments to the attention of all doctors as they did their routine paperwork. Senior doctors could influence how summaries are written by modifying the text. Messages could be added, for example, to say that patients with a particular diagnosis should be asked to participate in some clinical study. The text could also be adapted to collect research data by turning the standard entry into a research form. The system is already set up in this way to provide codes from the International Classification of Diseases, ninth revision[4] (table I); the same can be done for codes from other classification systems, such as diagnosis related groups. Thus, administrative and research data can be collected with little extra effort by using a system which is in itself quicker and less tedious than traditional methods.

We thank Mr Jim Radcliffe and Mr Roger Steer of the Camberwell Health Authority finance department for their support and encouragement. We thank Drs J C French, M Kiln, I L Michell, R W Penny, G Rice, and M P Roseveare of Paxton Green Health Centre for allowing us to examine the summaries arriving at the practice, and Drs K W Pettingale and J F Martin for access to the medical records of their patients.

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(Accepted 29 September 1988)

Dose response relation to oral theophylline in severe chronic obstructive airways disease

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Abstract

***Objective*—To evaluate measurement of the trapped gas volume as a measure of respiratory function in patients with chronic obstructive airways disease and their response to treatment with theophylline.**

***Design*—Patients able to produce consistent results on testing of respiratory function spent two weeks having dosage of theophylline adjusted to give individual pharmacokinetic data. This was followed by random assignment to four consecutive two month treatment periods—placebo and low, medium, and high dose, as assessed by serum concentrations of theophylline. Respiratory function and exercise performance was assessed at the end of each two month period.**

***Setting*—Chest unit in district hospital.**

***Patients*—Thirty eight patients with chronic bronchitis and moderate to severe chronic obstruction to airflow were recruited; 33 aged 53-73 years completed the study.**

***Interventions*—Dosage of oral theophylline increased during two week optimisation period to 800 mg daily unless toxicity was predicted, when 400 mg was given. Targets for the steady state serum theophylline concentrations were 5-10 mg/l in the low dose period, 10-15 mg/l in the medium dose, and 15-20 mg/l in the high dose period.**

***Endpoints*—Respiratory function as measured by forced expiratory volume in one second, forced vital capacity, peak expiratory flow rate, slow vital capacity, and static lung volumes using helium dilution and body plethysmography from which trapped gas volume was derived. Exercise performance assessed by six minute walking test and diary cards using visual analogue scale.**

***Measurements and main results*—The forced expiratory volume in one second, forced vital capacity, and peak expiratory flow rate changed only slightly (about 13%) over the range of doses. There was a linear dose dependent fall of trapped gas volume from 1·84 l (SE 0·157) to 1·42 l (0·152), 1·05 l (0·128), and 0·67 l (0·102) during the placebo and low, medium, and high dose treatment periods. Mean walking distance increased by up to 55·6 m (20%). There was a modest improvement in dyspnoea as the dose of theophylline was increased. Side effects were mostly minor but they became more frequent as the dose was increased.**

***Conclusion*—The fall in trapped gas volume may reflect an improvement in peripheral ventilation (associated with treatment with theophylline) which is less apparent in the more common tests of lung function used in patients with chronic obstructive airways disease.**

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Introduction

The assessment of the efficacy of bronchodilator treatment in patients with asthma is fairly straightforward. Simple tests such as peak expiratory flow rate and forced expiratory volume in one second correlate well with symptoms and the clinical response to treatment. In contrast the measurement of response to treatment in "irreversible" chronic obstructive airways disease is more difficult. Improvement of symptoms is common in these patients when measurements such as peak expiratory flow rate and forced expiratory volume in one second remain unchanged. In a small study of patients recovering from an acute exacerbation of chronic obstructive airways disease clinical improvement was accompanied by a fall in functional residual capacity and "trapped gas volume" with negligible changes in peak expiratory flow rate, forced expiratory volume in one second, or forced vital capacity.[1] Trapped gas volume is the difference between total lung capacity measured by whole body plethysmography and that measured by helium dilution[2,3] and probably represents the volume of poorly ventilated areas of the lungs, perhaps best described as a ventilatory "slow space." Falls in trapped gas volume have been reported during recovery from acute severe asthma[1,4] and after treatment in the chronic phase.[2,5] Reports of deflation of the lungs after inhaled bronchodilators[6,7] would also be consistent with a fall in trapped gas volume, though in those studies helium dilution was not used to measure total lung capacity.

The use of theophylline in the management of chronic obstructive airways disease is controversial and published reports differ widely in their results.[8] Some are totally negative,[9] but several show minor spirometric improvements with inconsistent effects on symptoms and tolerance of exercise.[10-12] Others, apparently studying similar patients, have shown that even in the absence of spirometric changes theophylline reduced breathlessness[13] and the work of breathing especially during exercise.[14]

This study was therefore designed to look at changes in trapped gas volume during long term treatment with theophylline, comparing it with more conventional measurements of respiratory function and exercise tolerance.

Patients and methods

Patients with chronic bronchitis (Medical Research Council definition) and moderate to severe chronic obstruction of airflow were recruited. Patients excluded from the study were those with clinical or laboratory evidence of asthma or allergy, $\geq$15% improvement in forced expiratory volume in one second 20 minutes after inhaling 500 μg terbutaline sulphate, known sensitivity to methylxanthine, and severe cardiovascular or other disease that might interfere with exercise testing. Patients all gave their written informed consent, and the study was approved by the Pontefract Health Authority's ethical committee.

Over one full day patients performed all the various planned tests on three occasions. Only those able to provide technically satisfactory and consistent results continued in the study. During the next two weeks the dose of controlled release theophylline 400 mg tablets was gradually increased so that one tablet was taken twice daily for the last seven days except when toxicity was predicted, in which case half the dose was given. At the end of this period venous blood was drawn for measuring serum theophylline concentration 10-14 hours after the previous evening's dose. This concentration together with demographic and clinical characteristics of the patient and precise history of dose were used in Bayesian analysis to estimate each patient's pharmacokinetic variables,[15-17] which were then used to derive a precise dose regimen for each patient.

The patients were then entered into the first of four two month treatment periods with targeted mean steady state serum theophylline concentrations of 0 (placebo), 5-10 mg/l (low dose), 10-15 mg/l (medium dose), and 15-20 mg/l (high dose). The order of administration was randomised, and the dose changes were effected in a single blind manner with matching placebo tablets. At the end of each two month period the following measurements were made: serum theophylline concentration (timed to coincide roughly with mean steady state serum theophylline concentration), forced expiratory volume in one second, forced vital capacity, peak expiratory flow rate, maximal expiratory flow volume curves, slow vital capacity, carbon monoxide transfer factor in a single breath, and static lung volumes with helium dilution and body plethysmography. Exercise performance was assessed with a six minute walking test on level ground, and subjective assessments were recorded on diary cards on a visual analogue scale for dyspnoea.

The helium dilution of functional residual capacity was measured by the standard closed circuit rebreathing method (P K Morgan Ltd); a change of $<$0·05% in helium concentration over two consecutive 30 second periods was used as the criterion to end the test. Helium dilutions were measured twice, separated by at least 20 minutes, with the larger of the two values being recorded. A Gould 2000 autobox was used to measure plethysmographic lung volume as the mean of three satisfactory readings. Spirometric and flow volume variables were measured with a pneumotachograph (Lilly) with on line computer analysis of the resulting signal. No measurements were carried out within two weeks after an acute exacerbation. Other treatments such as inhaled sympathomimetics, ipratropium bromide, and oral or inhaled steroids were continued at a constant dose throughout the study except during exacerbations, when assessments were delayed until the other treatment was reduced to the dose on entry for a minimum of seven days. No other oral bronchodilators were allowed. All tests were performed at about the same time of day. Throughout the study patients recorded any "rescue" use of inhalers in addition to their regular prescribed dose and were asked to record their breathlessness on a 10 cm visual analogue scale together with any side effects every week.

STATISTICAL ANALYSIS

The design of the study was such that 16 of the patients were randomly allocated to the order of treatment by four identical Latin squares. The other patients were randomly allocated, but the allocation included more patients taking placebo in period four than would have occurred if Latin square designs had been used. This was a deliberate choice because in this severely disabled group of patients we predicted that some would deteriorate with placebo treatment and withdraw prematurely.

We carried out a preliminary analysis of data from the 16 patients whose randomisation provided a balanced design with analysis of variance for the four period crossover design. This showed that period effects and the interaction between period and dose were negligible. The data from all the patients could therefore be analysed with analysis of variance, in which the total sum of squares were partitioned into subject, dose, and residual components. When there was a distinct dose effect the dose sum of squares was further partitioned into orthogonal polynomial contrasts so that the shape of the dose response relation could be determined. The residuals from these analyses were treated for normality with the Shapiro-Francia test.[18] This suggested that some of the variables were not normally distributed, but in all instances this discrepancy seemed to be the result of a few extreme values, which had no apparent effect on the analysis.

Results

Of the 38 patients entered, 33 satisfactorily completed the study. The five withdrawals comprised three patients who did not wish to continue, one whose forced expiratory volume in one second rose unexpectedly and exceeded the entry criterion, and one who developed severe dyspepsia and after gastroscopic examination was found to have an active gastric ulcer. Table I shows the details of the baseline respiratory function in the 33 patients (three women) who completed the study. Their ages ranged from 53 to 73 (mean 61·2, SD 5·71), and their weight ranged from 43 to 105 kg (75·2, 14·80). As a result of clinical deterioration the two month period of placebo was stopped early in eight patients and the low dose period stopped in three patients. In a further five patients the high dose period was cut short as a result of side effects. Each of these curtailed treatment periods was longer than two weeks on the prescribed dose, and the measurements were completed before treatment was altered. All the results were included in the final analysis.

TABLE I—*Baseline lung function values in patients who completed trial expressed as % predicted (residual volume and total lung capacity, expressed as simple percentage ratio)*

Case No	Transfer coefficient	Forced expiratory volume in one second	Total lung capacity measured by whole body plethysmography	Residual volume/plethysmographic total lung capacity
1	100·0	44·5	110·5	55·9
2	118·4	44·8	118·5	56·3
3	91·9	30·2	121·1	62·4
4	100·6	38·2	123·3	65·2
5	69·7	32·4	133·2	75·4
6	77·5	23·9	122·8	76·8
7	119·7	25·9	151·2	71·2
8	106·9	44·0	137·0	67·4
10	79·5	19·9	118·0	81·2
11	55·7	14·7	135·9	78·8
12	107·3	50·6	100·0	73·1
13	100·0	12·1	137·0	81·0
14	61·6	18·3	126·9	78·3
15	69·0	35·0	129·0	62·8
16	134·0	21·5	132·5	65·6
17	92·3	16·7	110·5	80·0
18	103·5	44·4	96·1	62·4
19	83·1	17·1	100·0	75·8
20	69·4	23·1	142·9	69·7
22	86·4	29·7	122·6	72·8
23	50·0	16·5	144·7	80·7
24	100·0	43·5	75·0	50·4
25	86·0	15·0	120·0	80·6
26	86·6	35·0	130·4	70·8
28	82·4	50·5	121·2	73·6
29	96·6	24·8	134·8	72·3
30	120·9	16·2	128·8	77·2
31	109·8	23·5	146·5	82·9
32	53·6	15·7	164·8	72·3
33	88·2	29·4	130·3	73·1
35	22·8	21·1	152·7	77·9
36	27·3	25·6	136·9	75·0
38	90·6	54·0	118·9	51·7
Mean (SD)	86·1 (25·5)†	29·1 (12·4)	126·5 (17·8)	71·2 (13·9)

TABLE II—*Summary of analysis of all variables expressed as means (SE) with various doses of theophylline*

	Dose				Pooled SE	p Value of linear contrast
	Placebo	Low	Medium	High		
Dose (mg/day)		503 (30·3)	860 (37·4)	1194 (53·3)		
Serum theophylline (mg/l)		6·3 (0·37)	12·1 (0·33)	18·3 (0·52)		
Forced expiratory volume in one second (l)	1·00 (0·087)	1·00 (0·092)	1·08 (0·096)	1·13 (0·091)	0·167	<0·001
Forced vital capacity (l)	2·46 (0·130)	2·53 (0·129)	2·65 (0·117)	2·78 (0·128)	0·323	<0·001
Peak expiratory flow rate (l/min)	142 (12·7)	150 (13·1)	157 (13·1)	160 (12·3)	31·2	0·11*
Slow vital capacity (l)	2·53 (0·144)	2·75 (0·135)	2·96 (0·119)	3·16 (0·127)	0·337	<0·001
Total lung capacity measured by helium dilution (l)	6·75 (0·282)	7·07 (0·300)	7·27 (0·273)	7·57 (0·297)	0·489	<0·001
Functional residual capacity measured by helium dilution (l)	4·85 (0·240)	4·95 (0·288)	5·00 (0·259)	5·08 (0·271)	0·429	0·17*
Total lung capacity measured by whole body plethysmography (l)	8·58 (0·276)	8·50 (0·271)	8·32 (0·278)	8·23 (0·276)	0·311	<0·001
Functional residual capacity measured by whole body plethysmography (l)	6·76 (0·271)	6·53 (0·294)	6·28 (0·284)	6·22 (0·278)	0·455	<0·001
Trapped gas volume (l)	1·84 (0·157)	1·42 (0·152)	1·05 (0·128)	0·67 (0·103)	0·484	<0·001
Distance walked (m)	290 (25·5)	295 (26·7)	316 (26·6)	346 (26·7)	41·0	<0·001

*p Values from overall dose effect showed lack of significance so orthogonal contrasts were not fitted.

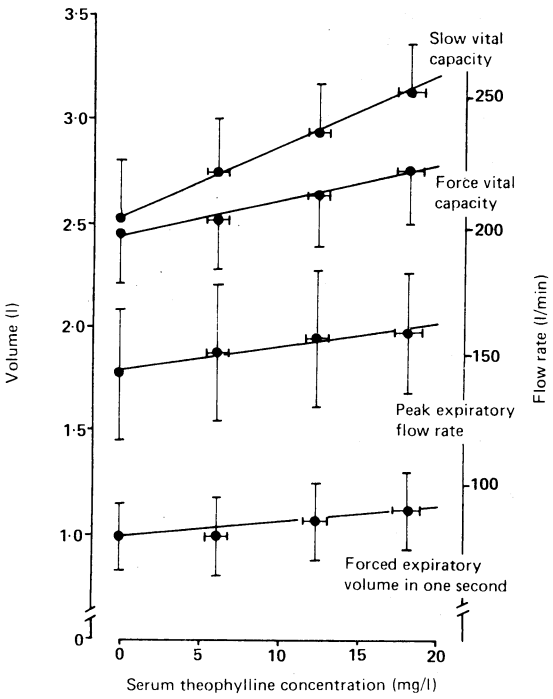

FIG 1—*Relation between dose and response for forced expiratory volume in one second, forced vital capacity, peak expiratory flow rate, and slow vital capacity. (Means and 95% confidence intervals)*

Table II summarises the results of the analysis of variance of the mean theophylline dose given and the resulting mean steady state serum concentrations for each dose, together with the other variables studied. p Values are given for the linear dose response relation for those variables in which the dose effect was significant and for the overall effect when $p>0·05$. Figure 1 shows that forced expiratory volume in one second, forced vital capacity, and peak expiratory flow rate changed slightly (though significantly) over the range of doses; the mean increase for all these, comparing high dose with placebo was about 13%, while the slow vital capacity showed a more distinct increase of 24·5%. The linear increase was highly significant for forced expiratory volume in one second, forced vital capacity, and slow vital capacity ($p<0·001$), but the overall dose effect was not significant for peak expiratory flow rate, so no estimate was made of the dose response relation. Figures 2 and 3 show a large, dose dependent linear fall in trapped gas volume made up of a fall in total lung capacity measured by whole body plethysmography and an increase in that measured by helium dilution, the contributions of the two lung volume measurements being one third and two thirds respectively. Overall trapped gas volume fell by 64%. Figure 3 shows that

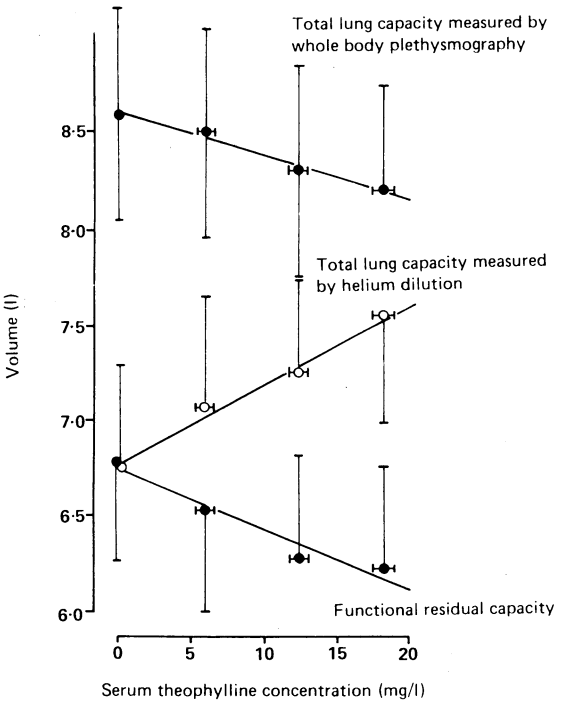

FIG 2—*Relation between dose and response for total lung capacity measured by whole body plethysmography, total lung capacity measured by helium dilution, and functional residual capacity. (Means and 95% confidence intervals)*

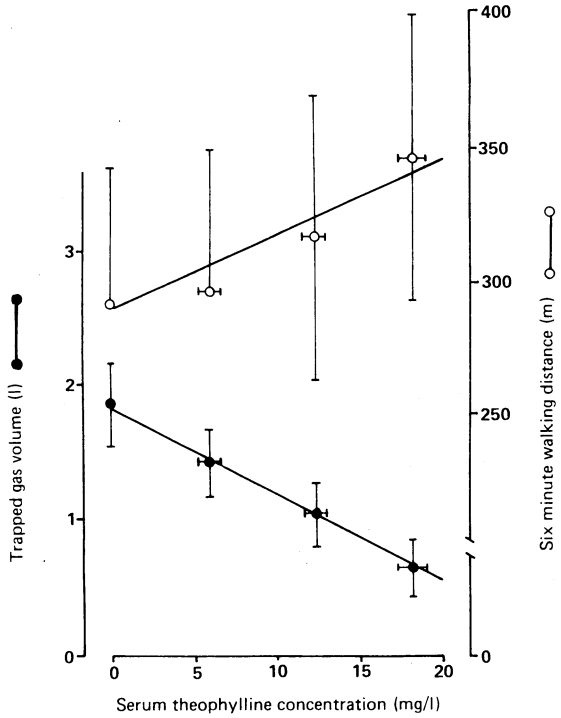

FIG 3—*Relation between dose and response for trapped gas volume and six minute walking distances. (Means and 95% confidence intervals)*

TABLE III—*Summary of linear relation between dose and response*

Variable	Slope of linear regression	SE of slope	Threshold (mg/l)*
Forced expiratory volume in one second (l)	0·0077	0·00214	22·6
Forced vital capacity (l)	0·0179	0·00414	14·5
Slow vital capacity (l)	0·0341	0·00432	8·2
Total lung capacity measured by helium dilution (l)	0·0438	0·00627	12·8
Total lung capacity measured by whole body plethysmography (l)	−0·0206	0·00399	26·8
Functional residual capacity (l)	−0·0310	0·00583	17·5
Trapped gas volume (l)	−0·0637	0·00621	4·9
Distance walked (m)	3·09	0·526	16·5
Visual analogue scale (mm)	0·4221	0·1147	19·7

*Serum theophylline concentration required to change placebo mean by two standard errors.

the fall was mirrored by a 20% overall increase in walking distance (55·6 m in total). All of these linear dose response relations were significant ($p<0·001$). There was no evidence that any of these relations were curved.

Table III quantifies the linear dose response, showing the regression coefficient and its standard error and the serum theophylline concentration required to change the placebo mean for each variable by twice its standard error. A two standard error change in trapped gas volume and slow vital capacity was achieved by 4·9 and 8·2 mg/l of serum theophylline respectively, which are close to the mean concentration achieved with the low dose. An increase of two standard errors in forced vital capacity and total lung capacity measured by helium dilution was achieved with 14·5 and 12·8 mg/l respectively, which reflect the mean concentration achieved at the medium dose. The other variables were changed by two standard errors with serum theophylline concentrations that were close to the high dose or higher than concentrations achieved in this study. This was especially true for forced expiratory volume in one second and total lung capacity measured by whole body plethysmography.

Table IV shows subjective assessment as measured by scores on the visual analogue scale for dyspnoea and "rescue" use of inhalers and includes mean scores for the last four diary entries from each treatment period.

TABLE IV—*"Rescue" use of bronchodilators and visual analogue scale for dyspnoea*

Treatment period	No of patients	Mean (SD) visual analogue scores (mm)*
Placebo	22	50·5 (19·7)
Low dose	19	49·2 (19·1)
Medium dose	12	54·6 (22·2)
High dose	10	57·3 (22·2)
	$\chi^2_3=11·75$; $p<0·008$	Linear dose response $p<0·001$

*0=Extremely breathless, 100=not at all breathless.

There was a modest but significant ($p<0·001$) improvement in subjectively recorded dyspnoea and a significant ($p<0·001$) reduction in the "rescue" use of bronchodilators as the dose of theophylline was increased. Table III shows that a serum theophylline concentration of 19·7 mg/l was required to change the placebo mean by twice its standard error.

In the 33 patients who completed the study side effects were fairly minor but became more frequent as the dose increased (Table V).

TABLE V—*Side effects experienced during trial**

Treatment period	Side effects
Placebo	Dyspepsia (one)
Low dose	Nausea (one), insomnia (one)
Medium dose	Dyspepsia (three)
High dose	Dyspepsia (four), nausea (one), headache (one), cramp (one), cramp and tremor (one), cramp and dyspepsia (one)

*Some patients experienced more than one side effect.

Discussion

In this group of patients with severe chronic obstruction of airflow we showed improvements in a variety of physiological variables related to the carefully titrated dose of oral theophylline. Changes in the most commonly used measurements—forced expiratory volume in one second, forced vital capacity, and peak expiratory flow rate—were small and unlikely to be considered important in clinical practice. The slow vital capacity improved to a greater extent, as has been described previously,[19] but the largest change was

seen in the trapped gas volume. As this is a compound function of two variables (total lung capacity measured by whole body plethysmography and that measured by helium dilution) which, in this context, changed in opposite directions, the volume clearly gives a large "signal" that may be valuable in studies of this type of patient. We did not measure the variability of this volume but, though this is likely to be greater than most of the other variables, figure 3 shows that at each dose point it was relatively small, and the analysis took this into account.

We suggest that the increase in total lung capacity measured by helium dilution, which made up some two thirds of the fall in trapped gas volume, was a result of small airway dilatation leading to improved ventilation of previously poorly ventilated areas of the lung. This might be explained purely in terms of relaxation of smooth muscle or it might be due to an anti-inflammatory effect of theophylline.[20] Explaining the fall in total lung capacity measured by whole body plethysmography is more complex and may be affected by the error inherent in assuming that mouth pressure is equal to alveolar pressure.[21,22] When limitation of the airflow is present a pressure gradient may exist with the effect that alveolar pressure is underestimated, which results in an erroneously high measurement of total lung capacity measured by whole body plethysmography. As the limitation of the airflow improves this gradient lessens and the measurement may fall. Even if this explains the entire change in the measurement, this artefact remains a function of the degree of airway obstruction (particularly the small airways) and as such will still have relevance in the assessment of these patients.

The falls in trapped gas volume (and functional residual capacity) are likely to improve the mechanical advantage of the diaphragm and chest wall muscles and may well explain many of the reported effects of xanthines on the respiratory muscles[23-26] without having to propose a direct effect of the drugs on muscle contractility or fatiguability. The suggestion that trapped gas volume may be clinically important is supported by the improvement in six minute walking distance and by the reduction in "rescue" use of bronchodilators and dyspnoea scores. Weekly diary scores of dyspnoea are probably a poor method of assessing subjective breathlessness, and the use of the visual analogue scale immediately after the exercise test may have better reflected efficacy.[27]

Changes in the physiological variables measured occurred continuously over the whole of the serum theophylline concentration range, with the greatest effect being seen at the highest mean steady state concentration (18·3 mg/l). As expected, most side effects were seen at this concentration, and changes of two standard errors in such indices as slow vital capacity and trapped gas volume were achieved at serum concentrations of 4·9 and 8·7 mg/l, suggesting that definite clinical improvement may well be obtained at doses much lower than those generally recommended. This observation is in keeping with much anecdotal clinical experience. In addition, other drugs such as corticosteroids and inhaled bronchodilators are likely to have similar effects and may thus be used in combination with lower doses of theophylline.

Many published reports have, in our opinion, depended too heavily on the cheapest and most readily available tests—namely forced expiratory volume in one second, forced vital capacity, and peak expiratory flow rate. Clearly, they are not particularly sensitive measures of change in this group of patients, and while measuring trapped gas volume is expensive and difficult, slow vital capacity is fairly easy and should be used more widely. We believe that the present work reports objective measurements of lung function and explains the improvement of symptoms seen by some doctors in so called irreversible disease. The corollary of this is that patients should not be classed as untreatable simply because of a failure to show some arbitrary response to one of these unsatisfactory tests. We should perhaps be more willing to trust careful clinical observations and the subjective improvement of our patients.

We thank Ms J F B Altman, consultant statistician for her help and advice with analysis; Mrs Nicola Hollands and Mrs Denise Humphrey for typing the manuscript; and the staff of Pontefract General Infirmary.

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(Accepted 6 September 1988)